WO 01/13929
PCT/CA00/00949

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
CÔTÉ, France
Swabey Ogilvy Renault
Suite 1600
1981 McGill College Avenue
Montréal, Québec H3A 2Y3
CANADA

Date of mailing (day/month/year) 01 March 2001 (01.03.01)	
Applicant's or agent's file reference 14226-3PCT	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/CA00/00949	17 August 2000 (17.08.00)	20 August 1999 (20.08.99)

Applicant
CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AG,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CR,CU,CZ,DE,DK,DM,DZ,EA,EE,EP,ES,
   FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,
   MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   01 March 2001 (01.03.01) under No. WO 01/13929

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer J. Zahra
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/13929 A1

(54) Title: ANTINEOPLASTIC EXTRACT FROM *ACHILLEA MILLEFOLIUM*

(57) Abstract: The present invention relates to isolated and purified plant extracts. There is provided an isolated and purified extract from *Achillea millefolium* to treat and prevent cancer. The purified fractions were administered to animals in which cancer was induced. The fractions demonstrated antimetastatic activity. Molecules contained in the fractions may also be used to treat and prevent cancer.

ANTINEOPLASTIC EXTRACT FROM *ACHILLEA MILLEFOLIUM*

BACKGROUND OF THE INVENTION

(a) Field of the Invention

The invention relates to isolated and purified plant extracts, and more particularly to one from *Achillea millefolium* to treat and prevent neoplastic disorders.

(b) Description of Prior Art

Yarrow is an important member of the *Asteraceae* branch of the *Compositae*, the daisy family. Common names for yarrow include milfoil staunch weed, nosebleed, soldier's herb, carpenter's wort, thousand weed, woundwort, bloodwort boomadaran and knight's milfoil. There are about 100 different species of yarrow that grow mainly in temperate region of the world. Yarrow, or *Achillea millefolium*, is said to have been used by the Greek hero Achilles to stop the bleeding of his warrior's wounds.

Yarrow (*Achillea millefolium* LINNAEUS) is used as a medicinal plant in different parts of the world, as an haemostatic, emmenagogue, antipyretic and diaphoretic in cases of common cold.

An infusion is generally made from *Achillea millefolium*, which is also used for lack of appetite, cramps, flatulence and other stomach-related disorders. Aboriginal people and pioneers also used yarrow as a tea to treat digestive disorders and fevers and as a poultice to treat cuts and burns, and chewed the leaves to relieve toothache pain. Yarrow has long been associated with the healing of wounds and the steeming of blood flow. The existing literature indicates that yarrow improves colon and liver function, is good against anemia, liver disease, skin disease, eczema, liver, psoriasis and rashes, as well as for treating cold, flu, fever, hypertension, painful menstruation

and bleeding. The value of yarrow as an anti-spasmodic and diuretic agent, as well as an anti-inflammatory and antiseptic compound, has been demonstrated.

The use of yarrow tea against cancer is known. For example, in Iran, people have been using yarrow tea for cancer for several hundreds years. Yarrow tea has been used in different parts of the world for centuries without manifesting toxicity or side effects, and some cancer patients in the United States and Canada have been taking yarrow as an alternative medicine. However, no proven anticancer activity has been reported.

Antitumor sesquiterpenoids were recently identified and isolated as methyl esters from *Achillea millefolium*, namely achimillic acids A, B, and C,. These compounds are active against mouse P-388 leukemia cells *in vivo*.

Known constituents of yarrow are essential oils, namely cineol, proazulene and achilleine.

Neoplastic disorders such as cancer are treated with agents which are generally toxic with severe side-effects.

It would be highly desirable to be provided with a substantially pure biologically active fraction isolated from *Achillea millefolium* that would have an antineoplastic activity, and that could be used to treat or prevent diseases such as cancer.

SUMMARY OF THE INVENTION

One aim of the present invention is to provide purified biologically active fractions isolated from *Achillea millefolium* that may be used to treat or prevent disorders such as cancer.

In accordance with the present invention there is provided a substantially pure biologically active

extract isolated from *Achillea millefolium*, said extract having an antineoplastic activity.

In accordance with one embodiment of the present invention, the extract consists of a crude methanol extract.

In accordance with another embodiment of the present invention, there is provided the use of such an extract for the preparation of a medicament for the treatment and/or prevention of a neoplastic disorder, such as cancer.

In accordance with another embodiment of the present invention, there is provided an antineoplastic composition to treat and/or prevent cancer, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

In accordance with another embodiment of the present invention, there is provided a method for treating and/or preventing a cancer in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.

The composition may be administered to a patient susceptible of developing or suspected of having a cancer, in an amount efficient to treat or prevent the cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the tracing obtained with the analytical HPLCs of the extracts;

Fig. 2 illustrates the fractions obtained with a large scale;

Fig. 3 illustrates a dose-response relationship for a methanol extract; and

Fig. 4 illustrates a dose-response relationship for fractions of methanol extracts.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided purified biologically active fractions isolated from *Achillea millefolium* to treat diseases such as cancer.

Fractions from *Achillea millefolium* LINNAEUS have been isolated. The purified fractions were administered to animals in which cancer was induced. No toxicity was observed at the doses administered. Moreover, the isolated organic soluble fractions have antimetastatic activity in a mouse cancer model. The isolated active fractions contain biologically active molecules that may be used to treat diseases including cancer.

More particularly, the crude methanol fraction had a good antimetastatic activity in the Lewis lung carcinoma model.

The animal model published by Tozyo et al. (*Chem Pharm Bull*, 1994, **42**:1096-1100) consists of a mouse leukemia P388 cell model. Tozyo et al. (supra) injected both cells and drugs intraperitoneally. This does not mimic physiological/pharmacological conditions observed in human cancer. Indeed, the conditions in Tozyo et al. resemble that of a petri dish where both the target and the drug are in direct contact. According to the present invention, the cells are injected subcutaneously to the Lewis lung carcinoma model. The cells then invade a distant site, such as lung, and form metastases. The test article is given by intraperitoneal route. Accordingly, the active

component(s) need to be absorbed, perhaps metabolized, before acting on primary tumors and/or metastases. This is closer to human disease in term of the growth versus multistep mechanisms of invasion.

As may be seen in Fig. 3, a dose-response relationship was observed.

As may be seen if Fig. 4, the E1, E2 and E4 fractions were the most active in inhibiting lung metastases.

Molecule(s) responsible for the biological activity of the extracts may be identified and characterized. The(se) molecule(s) may then be used to treat or prevent cancer, leukemias, as well as other diseases.

The fractions and molecules contained therein are advantageous over the whole plant or teas made from the plant.

The present invention will be more readily understood by referring to the following examples which are given to illustrate the invention rather than to limit its scope.

EXAMPLE I

Fractionation

Dried plant was grounded, and then stirred in methanol at 25°C for 48h. The resulting extract was filtered and treated with fresh methanol for another 48h. The combined extracts were filtered, evaporated and analyzed by HPLC. Analytical HPLC (Waters™ 600, Photodiodearray™ 996) was performed with two Whatman Partisil™ 10 ODS-2 analytical columns in series (4.6 x 250 mm). The gradient used consisted of 25-100% acetonitrile in water, 50 min gradient at a flow rate of 1 ml/min. Three fractions were identified according to retention times, namely the fractions 0-10, 11-22

and 23-60. The tracing of this analytical HPLC is shown in Fig. 1.

A large scale was then used. Briefly, 2 grams from methanol extract were dissolved in glass-distilled methanol and filtered, and three separations were performed with one Partisil™ 10 ODS-2 MAG-20 preparative column (22 x 500 mm) with the following gradient: 25-100% acetonitrile in water, 50 min. gradient at a flow rate of 18 ml/min. Four fractions were collected for each injection according to the following retention times: F1: 4.63-15.9; F2: 15.9-24.4; F3: 24.4-40.2; and F4: 40.2-60. The fractions are shown in Fig. 2.

The fractions were freshly solubilized in ethanol (final concentration is less than 20% of distilled water), and immediately used for *in vivo* studies or stored at -80°C.

EXAMPLE II

Lewis lung carcinoma (LLC) cell line and cell culture

The Lewis lung carcinoma (LLC) clone, M47, with a high metastatic potential to the lung, was established and characterized (Brodt P, *Cancer Res.*, **46**: 2442, 1986). These cells were confirmed free of mycoplasma infection. Cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin, under 5% CO_2. Cells were passaged twice a week. Stocks of cells were generated and stored as early passages (passage no. 8-10 received as passage no. 1, was considered the initial stock). Cells were then propagated and stocks of the same passages were established and stored in liquid nitrogen for further experiments.

For tumor induction, cells were grown to 70% confluence in complete medium and then collected using

trypsin-EDTA solution [0.05% trypsin, 0.53 mM EDTA-4Na in HBSS without Ca^{++}, Mg^{++}, and $NaHCO_3$; Cellgro no. 25-052-Li]. Cells were then centrifuged and washed three times with phosphate buffer solution [D-PBS, Ca^{++} and Mg^{++} free; Cellgro no. 21-031-LV], and resuspended at a dilution of 0.1-1 x 10^6 cells/0.1 ml. Viability was examined by Trypan blue staining and only flasks in which the viability was >95% were used for *in vivo* studies.

The C57BL/10 mouse strain from the research laboratories and incinerators was used, and access to the animal facility is strictly limited to animal users. The animal room has two doors, one serving as the entrance and the other providing direct access to washing, sterilization and incineration facilities, which allows an accurate adjustment of environmental parameters including temperature, humidity, ventilation and lighting.

EXAMPLE III

Tumor cell inoculation and treatment

Five mice were housed per cage and fed a diet of animal chow and water *ad libitum*. After one week of acclimatization, LLC cells were transplanted subcutaneously, as a suspension of tumor cells (2-5 x 10^5 viable cells/0.1 ml) in the axillary region of the right flank. Animals were subjected daily to general examination. Tumor growth was monitored every second or third day using calipers. Tumor were measured along the longest axis (length) and the perpendicular shortest axis (width) and the relative tumor volume (in cm^3) was calculated by the formula: [Length (cm) x (width cm)2]/2. When the tumor reached a size of 0.5-1.0 cm^2 (in approximately 2-3 weeks), the mice were randomized into three groups.

In the first group, the mice were subjected to surgery to remove the primary tumor. The mice were lightly anesthetized with Forane. The skin overlying the tumor was cleaned with betadine and ethanol in a laminar flow hood. A small skin incision (0.5-1.0 cm) was made using a sterile scalpel and the tumor was carefully separated from the normal tissues (skin and muscle). LLC (at an early stage of growth; 1-3 weeks) is a well-localized tumor, and separation was easy to achieve without any significant damage to normal tissues. The tumor was removed, weighed and fixed for histopathology purposes. The wound was closed with surgical stainless steel clips (Autoclips™; 9 mm; Clay Adams, Inc., Parsippany, NJ). The site was further disinfected with Betadine™ and the animal was housed as described earlier.

In the second group, the mice were randomized after surgery into groups of 5 per cage. The cages were randomly assigned to specific experimental groups. The mice were then labeled by numbers using the "ear punching" method. Mice were checked daily to ensure the absence of infection. Animals with disconfort were sacrified immediately. An additional extra-group of control mice was included to determine the optimal timing for sacrifice in order to obtain a significant number of well localized lung metastases. The second group was subjected to the same experimental procedure as the first group, with the exception of drug treatment. Based on the second group, a period of two weeks after removal of the primary tumor was sufficient to obtain an average of 20-30 nodules on the lung surface. Therefore, a two-week period after primary tumor removal was used to sacrify treated mice.

EXAMPLE IV

Dosing schedule and treatment

Drugs were given by intraperitoneal (ip) route (0.5 ml per animal) in daily administration after tumor cell inoculation. Control animals were given the same volume of saline solution (0.9% sodium chloride; Abott Laboratories, lot no. 12 455 WS). The dose of each drug was normalized to an average of 20 g/body weight/per animal. The schedules for drug treatment were based upon conditions described in Figs. 3-4.

EXAMPLE V

Animal sacrifice, tumor/organs preparation

At the end of each experiment, for a total of 5-8 weeks, animals were sacrified in a CO_2 chamber and autopsied. Tumors, organs or both were removed under sterile conditions using a laminar flow hood. Tumors were weighed. Organs (5/group) were examined for gross pathological changes and then fixed in 10% formalin. Lungs were fixed in 10% Bouin's fixative diluted in a formalin solution, and lung surface metastases were counted using a stereomicroscope at 4x magnification or a magnifying-glass.

EXAMPLE VI

Statistical analysis

The umpaired Student t-test was used to compare statistical significance among various groups.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following,

in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

WHAT IS CLAIMED IS:

1. A substantially pure biologically active extract isolated from *Achillea millefolium*, said extract having an antineoplastic activity.

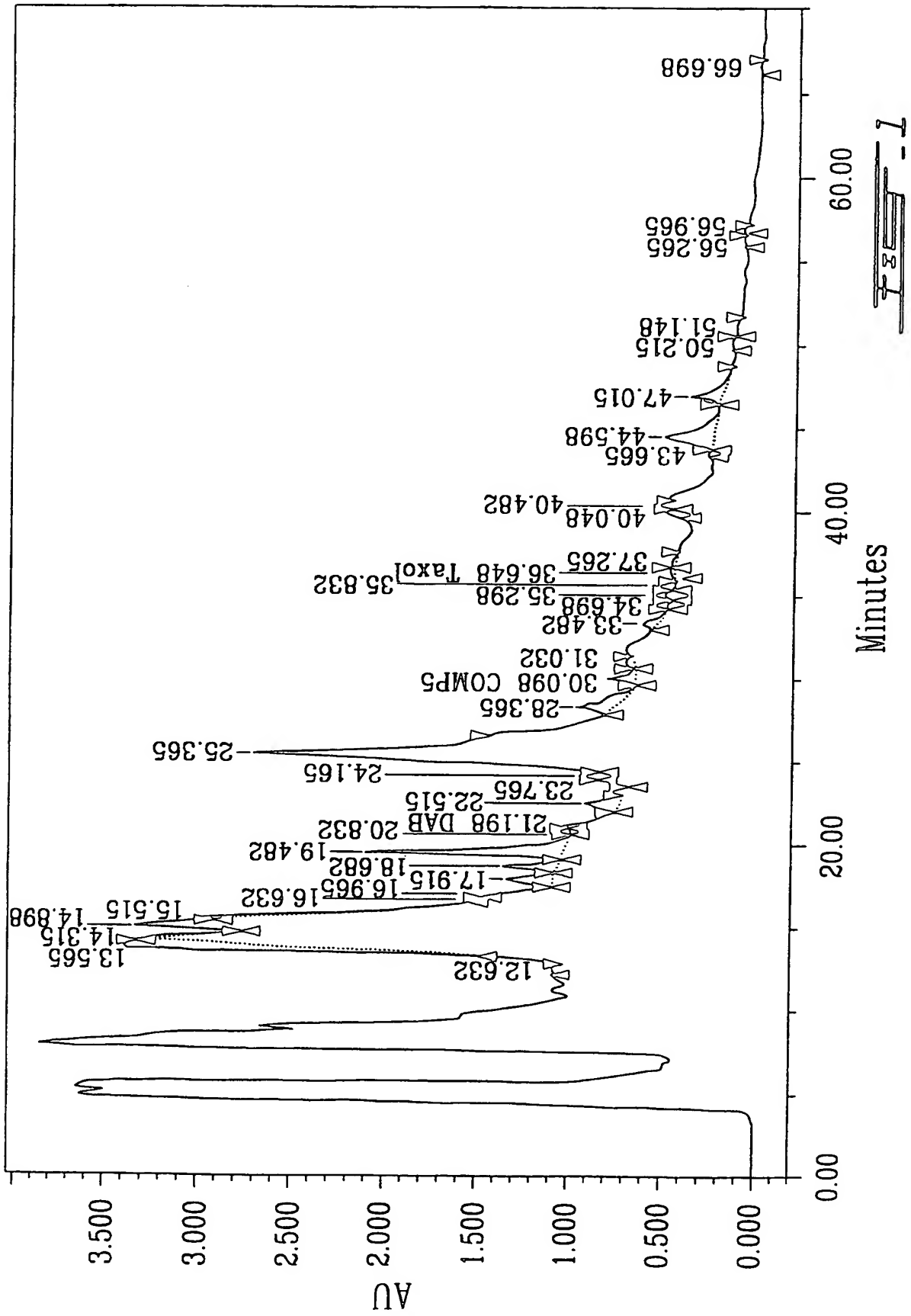
2. An extract according to claim 1, said extract consisting of a crude methanol extract.

3. The use of an extract according to claim 2, for the preparation of a medicament for the treatment and/or prevention of a neoplastic disorder.

4. The use of an extract according to claim 3, wherein said neoplastic disorder is cancer.

5. An antineoplastic composition to treat and/or prevent cancer, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

6. A method for treating and/or preventing a cancer in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.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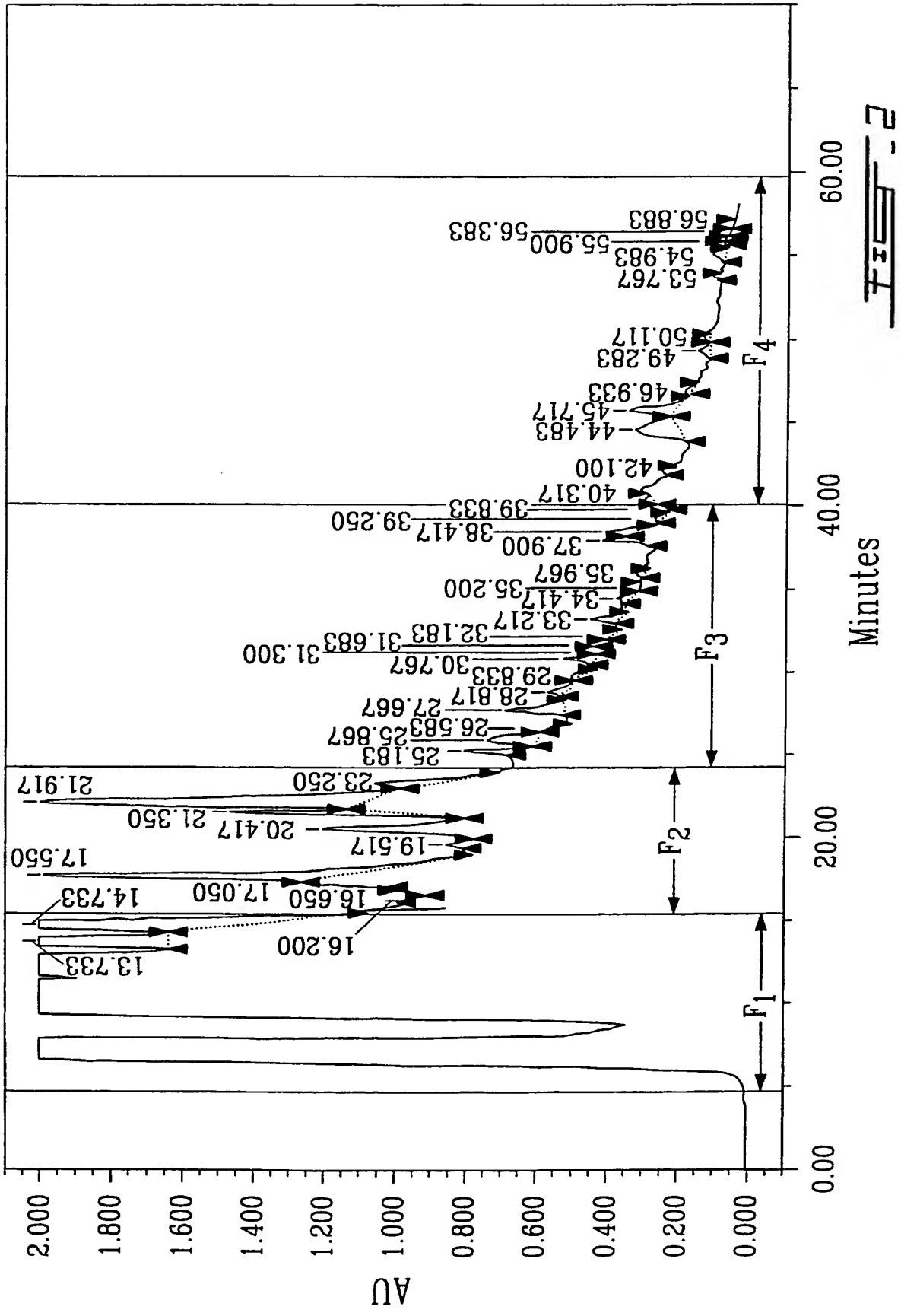
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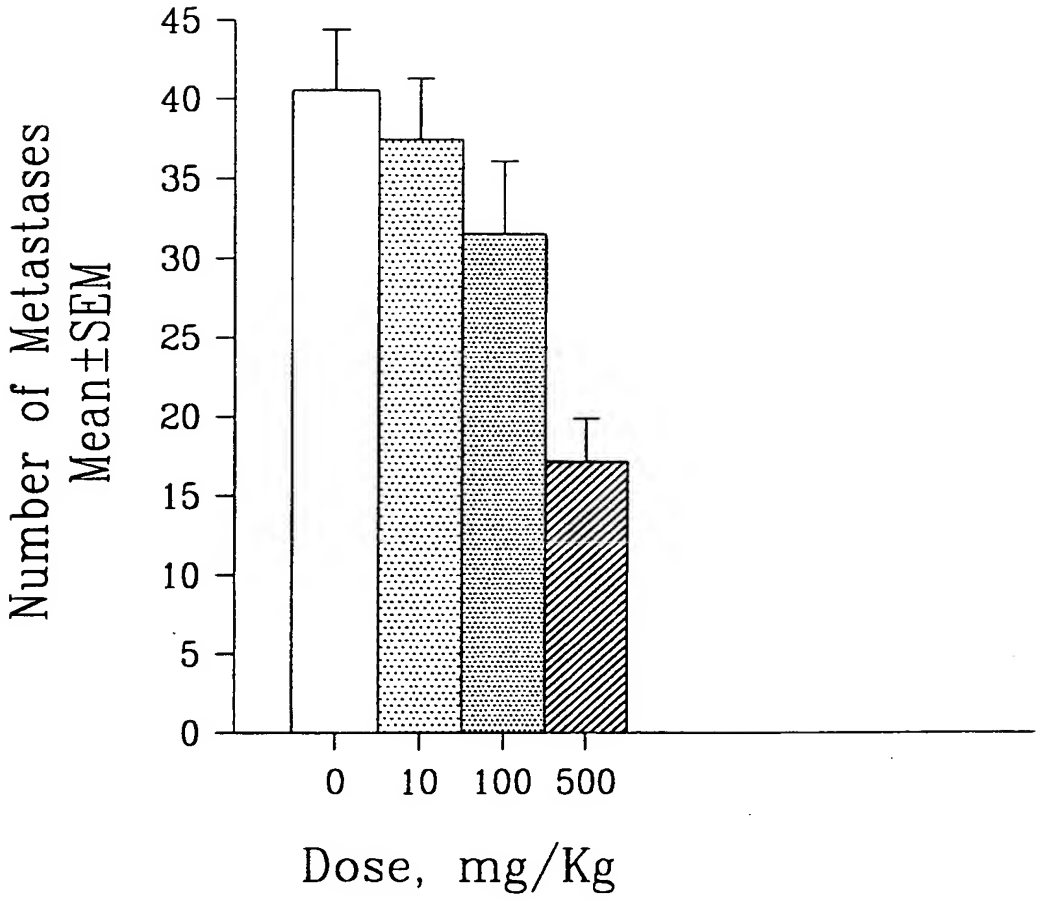
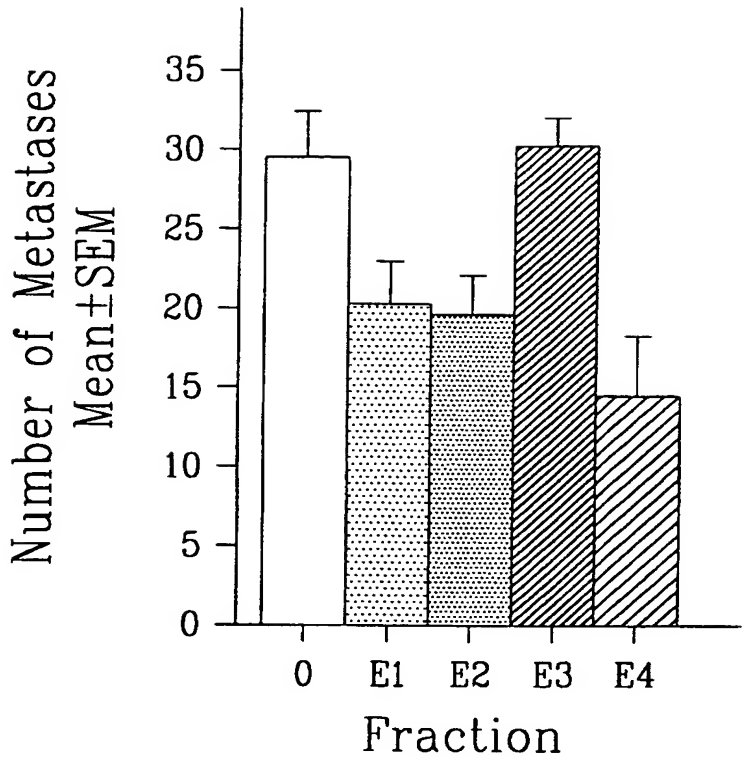
FIG. 2



7 ip administrations every second day
For each group n=10
No drug-related death was observed

FIG. 3



E1: 100mg/Kg, 7 ip administrations every second day
E2: 100mg/Kg, 7 ip administrations every second day
E3: 100mg/Kg, 7 ip administrations every second day
E4: 100mg/Kg, 7 ip administrations every second day

ip = intraperitoneal
For each group n=6
No drug-related death was observed

FIG 4

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/CA 00/00949

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, FSTA, CAB Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 282 (C-446), 11 September 1987 (1987-09-11) & JP 62 081349 A (SHIONOGI & CO LTD), 14 April 1987 (1987-04-14) abstract	1-6
X,P	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 13, 30 November 1999 (1999-11-30) & JP 11 236334 A (NISSIN FOOD PROD CO LTD), 31 August 1999 (1999-08-31) abstract	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	21/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rempp, G

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 6

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern· ·al Application No
PCT/CA 00/00949

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62081349 A	14-04-1987	JP 1931641 C	12-05-1995
		JP 6057674 B	03-08-1994
JP 11236334 A	31-08-1999	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SWABEY OGILVY RENAULT
1981, Avenue McGill College
Bureau 1600
Montréal, Québec H3A 2Y3
CANADA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	27.11.2001
Applicant's or agent's file reference 14226-3PCT FC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00949	17/08/2000	20/08/1999

Applicant
CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Hundt, D Tel.+49 89 2399-8042

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14226-3PCT FC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00949	17/08/2000	20/08/1999

International Patent Classification (IPC) or national classification and IPC
A61K35/78

Applicant
CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/03/2001	27.11.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Smetankine, L
Telephone No. +49 89 2399 8466

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00949

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-10	as originally filed				

Claims, No.:

1-5	as received on	19/11/2001	with letter of	13/11/2001	

Drawings, sheets:

1/4-4/4	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5.

because:

☒ the said international application, or the said claims Nos. 5 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 4,5

	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
see separate sheet

POINT III:

Claim 5 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

POINT V:

1. A crude methanol extract of Achillea millefolium (Am), a pure biologically active extract of Am having an antitumour activity is described by the first document cited by the Search Report- Patent Abstracts of Japan, vol.11, n°282 (C-446), 1987- see abstract, thus claims 1 to 3 seem to lack novelty.

   A composition containing a pure extract isolated from Am and a suitable carrier for the treatment of tumours does not involve inventive step because it is a matter of routine for a skilled person to put a suitable carrier together an active substance such as Am which already known for its antitumour activity (see (1), thus claims 1 to 5 lack inventive step.

2. For the assessment of the present claim 5 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. A substantially pure biologically active extract isolated from *Achillea millefolium*, said extract having an antineoplastic activity.

2. An extract according to claim 1, said extract consisting of a crude methanol extract.

3. The use of an extract according to claim 2, for the preparation of a medicament for the treatment and/or prevention of a neoplastic disorder.

4. The use of an extract according to claim 3, wherein said neoplastic disorder is cancer.

5. An antineoplastic composition to treat and/or prevent cancer, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

6. A method for treating and/or preventing a cancer in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.

PATENT COOPERATION TREATY

REC'D 29 NOV 2001
IPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14226-3PCT FC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00949	17/08/2000	20/08/1999
International Patent Classification (IPC) or national classification and IPC A61K35/78		
Applicant CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12/03/2001	27.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Smetankine, L Telephone No. +49 89 2399 8466

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00949

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-10	as originally filed				

Claims, No.:

1-5	as received on	19/11/2001	with letter of	13/11/2001	

Drawings, sheets:

1/4-4/4	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5.

because:

☒ the said international application, or the said claims Nos. 5 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 4,5

	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-5
Industrial applicability (IA)	Yes:	Claims	1-5
	No:	Claims	

2. Citations and explanations
see separate sheet

POINT III:

Claim 5 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

POINT V:

1. A crude methanol extract of Achillea millefolium (Am), a pure biologically active extract of Am having an antitumour activity is described by the first document cited by the Search Report- Patent Abstracts of Japan, vol.11, n°282 (C-446), 1987- see abstract, thus claims 1 to 3 seem to lack novelty.

   A composition containing a pure extract isolated from Am and a suitable carrier for the treatment of tumours does not involve inventive step because it is a matter of routine for a skilled person to put a suitable carrier together an active substance such as Am which already known for its antitumour activity (see (1), thus claims 1 to 5 lack inventive step.

2. For the assessment of the present claim 5 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

WHAT IS CLAIMED IS:

1. A substantially pure biologically active extract isolated from *Achillea millefolium*, said extract having an anti-tumorogenic and anti-metastatic activity.

2. An extract according to claim 1, said extract consisting of a crude methanol extract.

3. The use of an extract according to claim 2, for the preparation of a medicament for the treatment and/or prevention of a malignant tumor and/or metastases thereof.

4. An anti-tumorogenic and anti-metastatic composition to treat and/or prevent malignant tumor and/or metastases thereof, said composition comprising a therapeutically effective amount of a substantially pure extract isolated from *Achillea millefolium* having antineoplastic activity, and a suitable carrier.

5. A method for treating and/or preventing a malignant tumor and/or metastases thereof in a patient, said method comprising administering to said patient a therapeutically effective amount of a substantially pure biologically active extract isolated from *Achillea millefolium* with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Intern ıal Application No
PCT/CA 00/00949

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, FSTA, CAB Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 282 (C-446), 11 September 1987 (1987-09-11) & JP 62 081349 A (SHIONOGI & CO LTD), 14 April 1987 (1987-04-14) abstract	1-6
X,P	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 13, 30 November 1999 (1999-11-30) & JP 11 236334 A (NISSIN FOOD PROD CO LTD), 31 August 1999 (1999-08-31) abstract	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	21/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rempp, G

Form PCT/ISA/210 (second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 6

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Intern ·al Application No
PCT/CA 00/00949

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62081349 A	14-04-1987	JP 1931641 C JP 6057674 B	12-05-1995 03-08-1994
JP 11236334 A	31-08-1999	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
14226-3PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00949	17/08/2000	20/08/1999
Applicant		
CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 6 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 6

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00949

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, BIOSIS, FSTA, CAB Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 011, no. 282 (C-446), 11 September 1987 (1987-09-11) & JP 62 081349 A (SHIONOGI & CO LTD), 14 April 1987 (1987-04-14) abstract ---	1-6
X,P	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 13, 30 November 1999 (1999-11-30) & JP 11 236334 A (NISSIN FOOD PROD CO LTD), 31 August 1999 (1999-08-31) abstract -----	1

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2000	21/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Rempp, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 00/00949

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62081349 A	14-04-1987	JP 1931641 C	12-05-1995
		JP 6057674 B	03-08-1994
JP 11236334 A	31-08-1999	NONE	

TITLE: Isolation of achimilic acid A lactone as antitumor agent

INVENTORS: Ishii, Hiroshi; Sakurai, Kensuke; Tojo, Takehiko

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62081379	A2	19870414	JP 1985-222371	19851004
JP 05052292	B4	19930805		

PRIORITY APPLN. INFO.: JP 1985-222371 19851004

ABSTRACT

The title compound (I), useful as an antitumor agent, was isolated from Achillea millefollium L. Crude I was extracted with MeOH from A. millefolium L. flowers and subsequently purified twice by silica gel chromatog. I given once at 2 mg/kg, i.p., increased the life span of mice with transplanted P388 leukemia by 38%, and when administered continuously for 5 days at 1 mg/kg, by the same route, 48%.